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Strategies and Synthetic Methods Directed Toward the Preparation of Libraries of Substituted Isoquinolines

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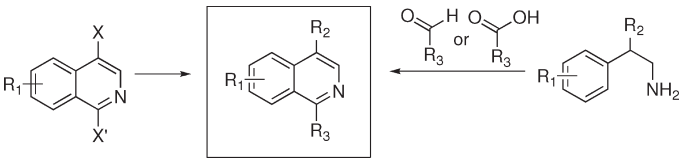

Strategies for the production of substituted isoquinoline libraries were developed and explored. Routes involving microwave-assisted variants of the Bischler−Napieralski or Pictet−Spengler reaction allowed for cyclization of substituted β-arylethylamine derivatives. The dihydroisoquinolines and tetrahydroisoquinolines thus generated could then be oxidized to their corresponding isoquinoline analogues. An alternate strategy, however, involving the preparation and activation of isoquinolin-1(2*H*)-ones is demonstrated to be a more practical, rapid, and efficient route to C1- and C4-substituted isoquinoline libraries.

Introduction

The isoquinoline ring is a common structural motif found in a variety of natural products and biologically active compounds. Access to this heterocyclic system has historically involved the application of either the Bischler−Napieralski or Pictet−Spengler reaction. The Bischler-Napieralski[1] reaction sees the conversion of an *N*-acyl-β-arylethyl amine into its corresponding dihydroisoquinoline then oxidation to the isoquinoline.[2] The Pictet−Spengler reaction[3] involves a Mannich-type reaction wherein a β-arylethylamine derivative is treated with an aldehyde under acidic conditions to generate an imine that can ring close to a tetrahydroisoquinoline and subsequently be oxidized to an isoquinoline.[4] Given that, in both cases, ring closure involves an electrophilic aromatic substitution, substrates that incorporate electron-rich aromatic systems tend to give the best yields. Most recently, protocols utilizing microwave irradiation in the Pictet−Spengler[5−10] and the Bischler−Napieralski[9] reactions have been described. Alternatively, the Larock isoquinoline synthesis involves the coupling of *o*-iodoaldimines and alkynes in the presence of a palladium catalyst to permit access to C3- and C4-substituted systems.[11−13]

Our interest in these reactions grew out of a need for a library of substituted isoquinolines required for biological studies currently being conducted in our laboratory. Specifically required were systems wherein substitution could be introduced at the C1 and C4 positions of the isoquinoline core (compound **i**, Figure 1). Two synthetic strategies were investigated: one wherein functionality is installed prior to cyclization (route a) and another wherein a suitable scaffold is activated then derivatized (route b). While both Bischler−Napieralski or Pictet−Spengler approaches allow for installation of functionality C1, introduction of C4 derivatization

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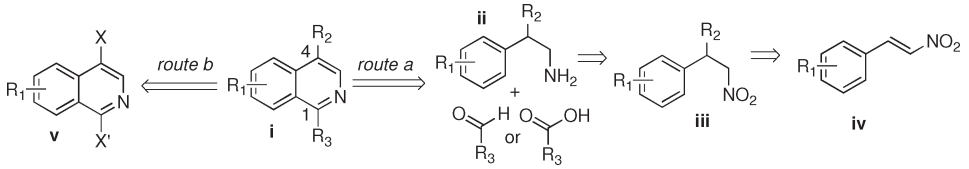


FIGURE 1. Approaches to substituted isoquinolines.

requires an appropriately functionalized β-arylethylamine (**ii**), which we envisioned could be prepared via a conjugate addition onto nitroalkene (**iv**), for example, to give **iii** followed by reduction. Alternatively, the desired isoquinolines could be generated from a heterocycle of the general type **v**, which could be prepared from an isoquinolin-1(2*H*)-one utilizing Bischler−Napieralski chemistry then activated and subsequently functionalized. Both approaches (routes a and b) were explored with an eye to the development of general, robust synthetic methods suitable for the synthesis of libraries of isoquinolines from readily available precursors.

Results and Discussion

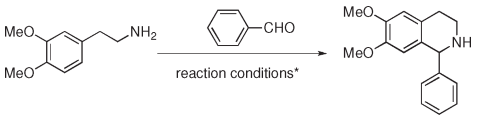
We focused our initial attention on the development of appropriate Bischler−Napieralski and Pictet−Spengler protocols for the cyclization of β-arylethylamines. Exploratory experiments revealed that classical reaction conditions for these transformations gave poor to moderate yields and were unsuitable for parallel synthesis approaches. Efforts were, therefore, focused on the development of microwave-assisted methods. A series of experiments was designed so as to determine the optimal reaction parameters for a microwave-assisted Pictet−Spengler reaction and were carried out so as to quickly ascertain the effects of solvent, acid concentration, temperature, and time (see Table 1). Entries 1−5 indicated that the reactions were best performed in the absence of solvent or in toluene.

Raising the reaction temperature from 90 to 140 °C (entries 6−9) allowed for a marked improvement on the yields. Simply increasing the reaction time from 15 min (entries 6 and 7) to 30 min (entries 8 and 9) provided the optimal set of reaction conditions and the best overall yields. Entries 10−17 illustrate the subtle interplay between equivalents of acid, temperature, and time. Xylene was shown to be a suitable solvent for the reaction as well (entry 18).

A number of protocols were investigated for the oxidation of the tetrahydroisoquinolines to their corresponding isoquinoline derivatives including those involving the use of IBX[14] and sulfur.[15] In our hands, the method described by Buchs and Brossi[16,17] involving dehydrogenation with Pd/C showed itself to be the most general and gave the best yields. For example, 1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**) was dehydrogenated with Pd/C in toluene to give 98% of the corresponding isoquinoline (**4b**).

With the microwave-assisted Pictet−Spengler and oxidation reactions in hand, sequential application of the two protocols (without isolation of the intermediate tetrahydroisoquinoline) was applied to the parallel synthesis of a small collection of isoquinolines (Scheme 1). The overall yields after both steps are shown and ranged from fair to very good. It should be noted that a number of commercially available microwave systems offer the ability to process samples in either a serial or parallel fashion enabling rapid production of compound libraries.

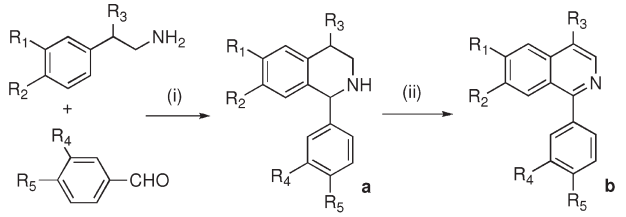
TABLE 1. Optimization of Reaction Parameters for the Microwave-Assisted Pictet−Spengler Reaction[a]



entry	solvent	equiv of TFA	temp (°C)	time (min)	% yield
1	ethanol	8	90	30	0
2	MeCN	8	90	30	trace
3	DMF	8	90	30	trace
4	toluene	8	90	30	12
5	none	8	90	30	20
6	none	8	140	15	81
7	toluene	8	140	15	75
8	none	8	140	30	98
9	toluene	8	140	30	89
10	toluene	2	140	15	15
11	toluene	2	140	30	45
12	toluene	4	140	15	50
13	toluene	4	140	30	71
14	none	8	160	10	89
15	toluene	13	140	15	98
16	none	13	140	15	92
17	none	16	120	30	98
18	xylene	8	140	30	96

[a]Reactions were carried out on a Biotage Initiator microwave synthesizer in a sealed microwave reaction vial with 1 mmol of amine and 1.2 mmol of aldehyde.

SCHEME 1. Synthesis of Isoquinolines Utilizing a Microwave-Assisted Pictet−Spengler Reaction[a]



where **1**: R_1=R_2=OMe; R_3=R_4=R_5=H; **6**: R_1=R_2=R_5=OMe; R_3=R_4=H;
2: R_1=R_2=OMe; R_3=R_4=H; R_5=F; **7**: R_1=R_2=OMe; R_3=R_4=H; R_5=Me;
3: R_1=R_2=OMe; R_3=R_5=H; R_4=OMe; **8**: R_1=OMe; R_2=R_3=R_4=R_5=H;
4: R_1=R_2=R_4=R_5=OMe; R_3=H; **9** R_1=R_2=OMe; R_3=Me; R_4=R_5=H
5: R_1=R_2=OMe; R_3=R_4=H; R_5=CN;

[a]Conditions: (i) 8 equiv of TFA, toluene, microwave at 140 °C, 30 min.; (ii) 10% Pd/C, toluene, reflux, 2−6 h.

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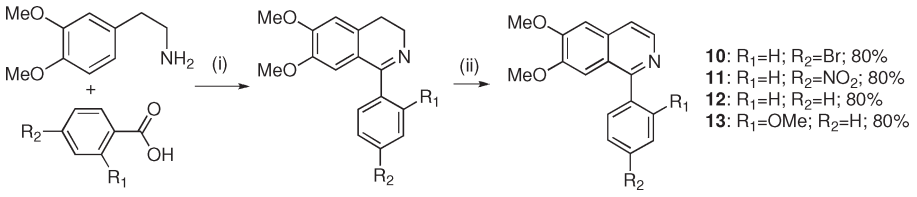
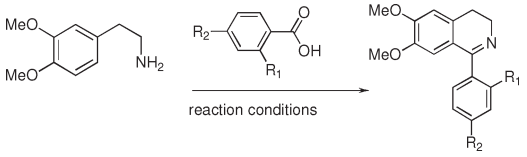
SCHEME 2. Synthesis of Isoquinolines Utilizing a Microwave-Assisted Bischler−Napieralski Reaction[a]



[a]Conditions: (i) $POCl_3$, toluene, microwave at 140 °C, 30 min.; (ii) Pd/C, 150 °C, 30 min.

TABLE 2. Optimization of Reaction Parameters for the Microwave-Assisted Bischler−Napieralski Reaction.[a]



entry	R^1	R^2	solvent	equiv of $POCl_3$	temp (°C)	time (min)	yield (%)
1	H	H	MeCN	4	120	30	23
2	H	H	MeCN	4	140	30	50
3	H	H	toluene	4	140	30	97
4	H	NO_2	MeCN	4	120	30	45
5	H	NO_2	MeCN	4	140	30	60
6	H	NO_2	toluene	4	140	30	85
7	H	Cl	MeCN	4	120	30	31
8	H	Cl	MeCN	4	140	30	74
9	H	Cl	toluene	4	140	30	79
10	H	Br	toluene	4	140	30	81
11	OMe	H	toluene	4	140	30	56
12	H	Br	toluene	6	140	30	82
13	H	Br	toluene	8	140	30	89
14	H	Br	toluene	10	140	30	89
15	H	Cl	toluene	10	140	30	79
16	H	NO_2	toluene	10	140	30	85
17	OMe	H	toluene	10	140	30	90
18	H	H	toluene	10	140	30	89

[a]Reactions were carried out on a Biotage Initiator microwave synthesizer in a sealed microwave reaction vial with 1 mmol of amine and 1 mmol of carboxylic acid.

The development of a microwave-assisted Bischler−Napieralski reaction protocol was then undertaken. Ideally, a reaction wherein the amide formation and cyclization to the 3,4-dihydroquinoline occurs in "one-pot" would be ideal. With use of 2-(3,4-dimethoxyphenyl)ethylamine and $POCl_3$, a series of exploratory reactions were carried out so as to quickly ascertain the effects of solvent, temperature, and time (see Table 2). Optimal conditions involved treating the amine and carboxylic acid with $POCl_3$ in toluene and irradiating the mixture in a microwave at 140 °C for 30 min. It is worth noting that carrying out the reaction above with conventional heating required upward of 8 h for complete consumption of starting materials.

Oxidation of the 3,4-dihydroisoquinoline derivatives to their corresponding isoquinoline derivatives using dehydrogenation with Pd/C in toluene (as used for the oxidation of tetrahydroisoquinolines) was slow and did not give full conversion of starting material. Yields obtained after 72 h of refluxing in toluene with Pd/C ranged between 40% and 60%. Comparable yields were obtained when 3,4-dihydroisoquinoline derivatives were heated in the presence of IBX[14] in DMSO at 45 °C for 24 h. While disappointing, the results were not unprecedented. A review of the relevant literature shows that these oxidations often require forcing conditions such as Pd/C in decaline at 230 °C[18] or MnO_2 in refluxing benzene.[19] The best results were obtained when the dehydrogenation was carried out with Pd/C in the absence of solvent and heating at 150 °C for 30 min.[20] For example, when 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline (Table 2, entry 18) was oxidized with this protocol, 97% of the corresponding isoquinoline was isolated.

With the microwave-assisted Bischler−Napieralski and oxidation protocols in hand, the two reactions were applied to the synthesis of a small collection of isoquinolines (Scheme 2, with overall yields reported). When the reaction was carried out with aryl acetic acid derivatives, however, facile air oxidation of the benzylic methylene resulted in the keto-imine product shown. Oxidation of these compounds allows for the series of acylisoquinolines shown in Scheme 3.

With the cyclization and oxidation procedures developed, the feasibility of the nitroalkene approach to substituted *β*-arylethylamines (route a) was examined. We found that the requisite nitroalkenes could be generated via an ultrasound-promoted, Henry condensation[21] and that there was ample literature precedence for conjugate addition onto the nitroalkenes.[22−24] While useful for the synthesis of individual isoquinoline derivatives, in practice, this chemistry is less than ideal for the preparation of large libraries of substituted isoquinolines mainly due to issues surrounding the conjugate addition onto the nitroalkenes, specifically, the relatively narrow scope of useful functionality that can be introduced at the C4-position using this approach. In addition, while oxidation of either the tetrahydroisoquinolines or the 3,4-dihydroisoquinoline could be achieved in excellent yields, the protocol with Pd/C does not lend itself to library synthesis. An alternate strategy (Figure 1, route b) with an isoquinolin-1(2*H*)-one scaffold as a starting point was, therefore, examined. This approach proved itself to be more practical and

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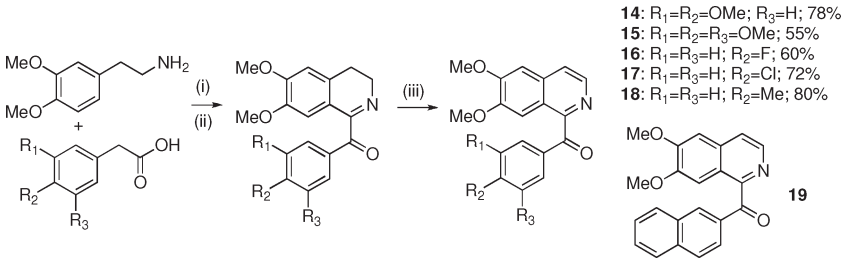
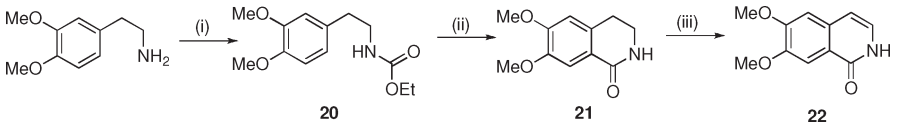
SCHEME 3. Microwave-Assisted Bischler−Napieralski Reactions with Aryl Acetic Acid Derivatives[a]



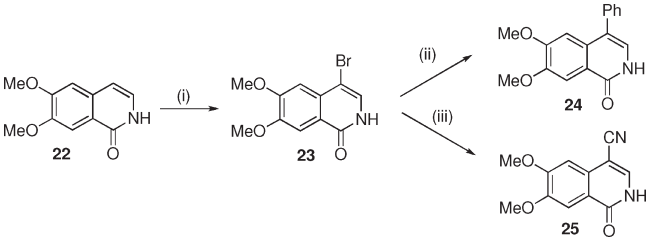
[a]Conditions: (i) $POCl_3$, toluene, microwave at 140 °C, 30 min.; (ii) air; (iii) Pd/C, 150 °C, 30 min.

SCHEME 4. Synthetic Route to 6,7-Dimethoxyisoquinolone[a]



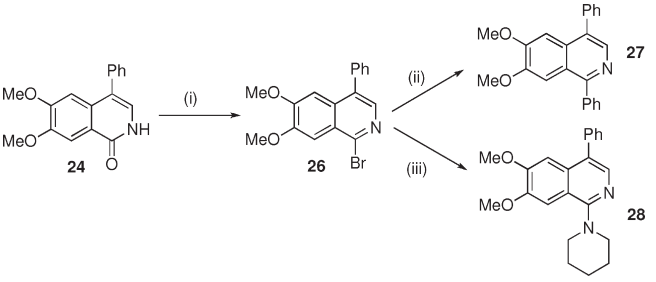
[a]Conditions: (i) ethyl chloroformate, TEA, DCM (96%); (ii) P_2O_5, $POCl_3$, hexamethyldisiloxane, microwave at 150 °C, 40 min (96%); (iii) Pd/C, 150 °C, 30 min (98%).

SCHEME 5. Access to C4-Substituted Isoquinolones[a]



[a]Conditions: (i) Br_2, AcOH (96%); (ii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, toluene, microwave at 90 °C, 30 min (98%); (iii) CuCN, 1-methylpyrrolidinone, microwave at 200 °C, 40 min (86%).

SCHEME 6. C1 Derivatization of 6,7-Dimethoxy-4-phenylisoquinolin-1(2*H*)-one[a].



[a]Conditions: (i) 3 equiv of $POBr_3$, DCM, microwave at 120 °C, 30 min (98%); (ii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, toluene, microwave at 90 °C, 30 min (95%); (iii) piperidine, NaO^{t}Bu, toluene, microwave at 180 °C, 30 min (64%).

also takes advantage of the Pd-catalyzed cross-coupling chemistry developed in our laboratory.[25−29]

6,7-Dimethoxyisoquinolone (**22**) was identified as a suitable building block for our initial studies. While a number of syntheses to the isoquinolin-1(2*H*)-one system have been reported,[30,31] a particularly attractive route takes advantage of chemistry developed by Chern and Li[32] and the dehydrogenation protocol developed above. As illustrated in Scheme 4, treatment of 2-(3,4-dimethoxyphenyl)ethylamine with ethyl chloroformate provided carbamate **20**, which could be cyclized smoothly in the presence of P_2O_5, $POCl_3$, and hexamethyldisiloxane by using microwave irradiation to give 6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**21**) in 95% yield. Finally, use of Pd/C allowed for oxidation to the desired **22** in 98% yield. Given the facile access to 3,4-dihydroisoquinolines demonstrated by Wang[33] and others, the approach should be applicable for the preparation of other isoquinolin-1(2*H*)-one scaffolds.

Protocols allowing for rapid and efficient activation and functionalization of the heterocycle were then explored. As presented in Scheme 5, bromination of **22** provides the vinylbromide **23**, a substrate capable of undergoing a variety of reactions permitting derivatization at C4. Palladium-mediated cross-coupling chemistry, for example, allowed for the arylation of compound **23** in 98% yield by using a Suzuki reaction to give **24** with a catalytic system incorporating the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (PA-Ph) ligand.[26−29,34] Alternatively, treatment of **23** with CuCN in 1-methylpyrrolidinone provided the 4-nitrile derivative (**25**) in 86% yield.

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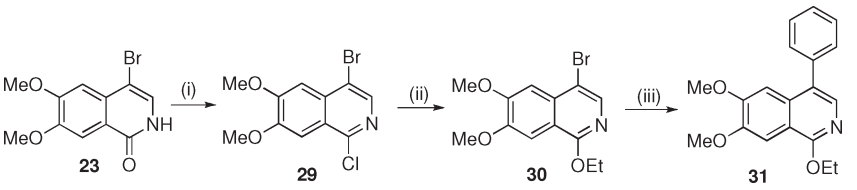
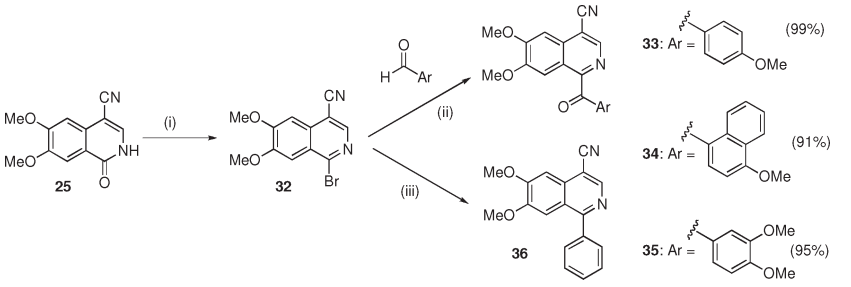
SCHEME 7. C1 and C4 Derivatization of 4-Bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one[a]



[a]Conditions: (i) $POCl_3$, microwave at 100 °C, 30 min (98%); (ii) NaOEt/EtOH, microwave at 90 °C, 30 min (87%); (iii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, toluene, microwave at 100 °C, 30 min (93%).

SCHEME 8. C1 Derivatization of 6,7-Dimethoxy-1-oxo-1,2-dihydroisoquinoline-4-carbonitrile[a]



[a]Conditions: (i) 3 equiv of $POBr_3$, anisole, microwave at 150 °C, 30 min (89%); (ii) 1,3-dimethylimidazolium iodide, NaH, DMF, room temperature, 1−2 h; (iii) Ph-$B(OH)_2$, Pd_2dba_3, PA-Ph, Cs_2CO_3, toluene, microwave at 90 °C, 30 min.

With functionality introduced at C4, activation of the C1 position was readily achieved via conversion to a bromoimine moiety. Treatment of 6,7-dimethoxy-4-phenylisoquinolin-1(2*H*)-one with $POBr_3$ in DCM using microwave irradiation (Scheme 6) yielded **26** in 98% yield. The bromoimine then serves a substrate for a number of reactions allowing for arylation (to give **27** via a Suzuki reaction in 95% yield) and amination (to give **28** in 64% yield).

Alternatively, chlorination of **23** with $POCl_3$ gives **29** (Scheme 7).[35] Taking advantage of the chemoselectivity at the two halogen sites allows for nucleophilic reaction at C1 (for example, treatment with ethoxide to give **30**) followed by cross-coupling at C4 to give **31**.

Another interesting route for derivatization at C1 involves nucleophilic aroylation[36,37] to give acylisoquinolines. As presented in Scheme 8, bromination of **25** in anisole using microwave irradiation allowed for the preparation of bromoimine **32** in 89% yield. This 1-bromoisoquinoline substrate could then be coupled with commercially available aromatic aldehydes in the presence of 1,3-dimethylimidazolium iodide to generate compounds **33**, **34**, and **35** in excellent yields. Finally, **32** could be used as a partner in a Suzuki coupling to give systems such as **36**.

Conclusions

Microwave-assisted variants of the Bischler−Napieralski or Pictet−Spengler reaction were developed and used in the production of isoquinolines. An alternate strategy presented involving the preparation and activation of isoquinolin-1(2*H*)-ones, however, is clearly a more practical, rapid, and efficient route to substituted isoquinoline libraries. Furthermore, the chemistry developed for derivatization allows for the installation of a diverse collection of vectors at the C1 and C4 position of the isoquinoline core and, therefore, a library capable of a more comprehensive exploration of chemical space. Work is currently underway to further determine the scope of the approach and prepare larger libraries of substituted isoquinolines by using this chemistry.

Experimental Section

General Procedure for the Microwave-Assisted Pictet−Spengler Synthesis of 1,2,3,4-Tetrahydroisoquinolines. Amine (1 mmol), aldehyde (1.2 mmol), TFA (8 mmol), and toluene (1 mL) were placed in a microwave vial, which was then capped and irradiated in a microwave for 30 min at 140 °C. The solvent was then evaporated under reduced pressure and the crude reaction mixture was suspended in cold water (3 mL), treated with aqueous NaOH (2 M) to pH 8, and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts was dried over Na_2SO_4, concentrated, and purified by flash column chromatography on silica gel with 3−5% MeOH in dichloromethane to afford the corresponding tetrahydroisoquinoline.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-phenylisoquinoline (1a): Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), benzaldehyde (100 μL, 1.2 mmol), and the general procedure, **1a** was obtained in 98% yield (264 mg, 0.98 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27−7.36 (m, 5H), 6.64 (s, 1H), 6.25 (s, 1H), 5.06 (s, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 2.77−3.25 (m, 4H), 1.80 (br , 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.6, 147.1, 144.6, 129.6, 128.9, 128.4, 127.6, 127.4, 111.4, 110.9, 61.3, 55.8, 41.7, 29.2; HRMS (CI) calcd for $C_{17}H_{20}NO_2$ (M + 1) 270.1495, found 270.1495.

General Procedure for the Synthesis of Isoquinolines via a Microwave-Assisted Pictet−Spengler/Oxidation Method. Amine (0.5 mmol), aldehyde (0.6 mmol), TFA (4 mmol), and toluene (1 mL) were placed in a microwave vial, which was then capped and irradiated in a microwave for 30 min at 140 °C. Additional

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(36) Yumiko, S.; Tomonori, T.; Akira, M.; Masayuki, S. *Chem. Pharm. Bull.* **2006**, *12*, 1653–1658.
(37) Suzuki, Y.; Ota, S.; Fukuta, Y.; Ueda, Y.; Sato, M. *J. Org. Chem.* **2008**, *73*, 2420–2423.

toluene (5 mL) was added and the reaction mixture was transferred to a vial containing 10% Pd/C (70 mg) in toluene (4 mL). The mixture was left to reflux for 2−12 h at which time the Pd/C was filtered off and the Pd/C residue was washed with hot toluene (20 mL). The solvent was evaporated under a reduced pressure and the residue was purified by flash column chromatography on silica gel with 2−5% MeOH in dichloromethane to obtain the isoquinoline derivatives.]

6,7-Dimethoxy-1-phenylisoquinoline (1b): Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), benzaldehyde (50 μL, 0.6 mmol), and the general procedure described, **1b** was obtained in 74% yield (98 mg, 0.37 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.49 (d, J = 5.6 Hz, 1H), 7.71 (dd, J = 5.8 and 2 Hz, 2H), 7.50−7.54 (m, 4H), 7.38 (s, 1H), 7.13 (s, 1H), 4.05 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.5, 152.8, 150.1, 141.6, 140.2, 133.9, 129.7, 128.6, 122.7, 118.9, 105.7, 105.1, 56.2, 56.0; HRMS (CI) calcd for $C_{17}H_{16}NO_2$ (M + 1) 266.1136, found 266.1103.

General Procedure for the Microwave-Assisted Bischler−Napieralski Synthesis of 3,4-Dihydroisoquinolines. Amine (1 mmol), carboxylic acid (1 mmol), $POCl_3$ (4 mmol), and toluene (2 mL) were placed in a microwave vial, which was then capped and irradiated in a microwave for 30 min at 140 °C. The solvent was then evaporated under reduced pressure and the crude reaction mixture was suspended in cold water (3 mL), treated with aqueous NaOH (2 M) to pH 8, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts was dried over Na_2SO_4, concentrated, and purified by flash column chromatography on silica gel with 3−5% MeOH in dichloromethane to afford the corresponding 3,4-dihydroisoquinolines.

3,4-Dihydro-6,7-dimethoxy-1-phenylisoquinoline (Table 2, Entry 3): Using 3,4-dimethoxyphenethylamine (166 μL, 1 mmol), benzoic acid (122 mg, 1 mmol), and the general procedure described, 3,4-dihydro-6,7-dimethoxy-1-phenylisoquinoline was obtained in 97% yield (259 mg, 0.97 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.58−7.63 (m, 2H), 7.41−7.45 (m, 3H), 6.80 (s, 1H), 6.78 (s, 1H), 3.95 (s, 3H), 3.84 (t, J = 7 Hz, 2H), 3.73 (s, 1H), 2.74 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.8, 151.0, 147.1, 139.1, 132.6, 129.4, 128.8, 128.2, 121.6, 111.7, 110.3, 56.2, 56.1, 47.6, 26.0; HRMS (CI) calcd for $C_{17}H_{18}NO_2$ (M + 1) 267.1293, found 268.1323

General Procedure for the Synthesis of Isoquinolines via a Microwave-Assisted Bischler−Napieralski Reaction/Oxidation Method (Scheme 2). Amine (0.5 mmol), carboxylic acid (0.5 mmol), $POCl_3$ (2 mmol), and toluene (2 mL) were placed in a microwave vial, which was capped and irradiated in a microwave for 30 min at 140 °C. The solvent was then evaporated under reduced pressure and the crude reaction mixture was suspended in cold water (3 mL), treated with aqueous NaOH (2 M) to pH 8, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts was dried over Na_2SO_4 and concentrated under a reduced pressure. Pd/C (70 mg, 10%) was then added to the residue, mixed together with a spatula, and heated to 150 °C for 30 min. The reaction mixture was cooled to room temperature and suspended in dichloromethane (20 mL). Pd/C was removed via filtration and the filtrate was concentrated before purification by flash column chromatography on silica gel with 2−3% MeOH in dichloromethane.

1-(4-Bromophenyl)-6,7-dimethoxyisoquinoline (10): Using 3,4-dimethoxyphenethylamine (83 μL, 0.5 mmol), 4-bromobenzoic acid (100 mg, 0.5 mmol), and the general procedure described, **10** was obtained in 80% yield (137 mg, 0.4 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.46 (d, J = 5.6 Hz, 1H), 7.50−7.69 (m, 5H), 7.29 (s, 1H), 7.13 (s, 1H), 4.05 (s, 3H), 3.88 (s, 3H); ^{13}C ($CDCl_3$, 50 MHz) δ 157.1, 152.9, 150.4, 141.5, 139.1, 134.0, 131.8, 131.4, 122.9, 122.5, 119.2, 105.2, 56.3, 56.1; HRMS (CI) calcd for $C_{17}H_{15}BrNO_2$ (M + 1) 344.0187, found 344.0208.

Ethyl 3,4-Dimethoxyphenethylcarbamate (20): To a solution of 3,4-dimethoxyphenethylamine (0.55 mL, 3.3 mol) and triethylamine (0.51 mL, 3.6 mmol) in DCM (10 mL) cooled at 0 °C was added ethyl chloroformate (0.35 mL, 3.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The precipitate formed was filtered and the filtrate was washed with distilled water (8 mL). The organic fraction was then dried over Na_2SO_4, concentrated, and purified by flash column chromatography on silica gel with 30% ethyl acetate in hexane to afford **20** in 96% yield (802 mg, 3.17 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.69−6.82 (m, 3H), 4.69 (br, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.39 (q, J = 7.0 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 1.21 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 156.6, 149.0, 147.7, 131.3, 120.7, 112.0, 111.4, 60.7, 55.9, 55.8, 42.2, 35.7; HRMS (CI) calcd for $C_{13}H_{20}NO_4$ (M + 1) 254.1348, found 254.1390.

3,4-Dihydro-6,7-dimethoxyisoquinolin-1(2*H*)-one (21): Ethyl 3,4-dimethoxyphenethylcarbamate (**20**) (229 mg, 1 mmol) was treated with $POCl_3$ (6 mL, 60 mmol), hexamethyldisiloxane (6 mL, 27.6 mmol), and P_2O_5 (892 mg, 6 mmol). The reaction mixture was capped and irradiated in a microwave for 40 min at 150 °C. The reaction mixture was concentrated and then poured on ice, neutralized with NaOH (2 M), and extracted with DCM. The DCM extract was dried over Na_2SO_4, concentrated, and purified by flash column chromatography on silica gel with 50% ethyl acetate in hexane to give **21** in 96% yield (199 mg, 0.96 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.57 (s, 1H), 6.67 (s, 1H), 6.17 (br, 1H), 3.58 (t, J = 6.6 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.4, 152.4, 148.2, 132.7, 121.5, 110.4, 109.7, 56.2, 40.7, 28.2; HRMS (CI) calcd for $C_{11}H_{14}NO_3$ (M + 1) 208.0927, found 208.0957.

6,7-Dimethoyisoquinolin-1(2*H*)-one (22): A mixture of 3,4-dihydro-6,7-dimethoxyisoquinolin-1(2*H*)-one (**21**) (198.8 mg, 0.96 mmol) and 10% Pd/C (100 mg) was ground to a fine powder before heating at 150 °C for 30 min. The mixture was suspended in DCM (100 mL) before filtering to remove the Pd/C. Evaporation of the solvent under reduced pressure yielded **22** in 98% yield (194 mg, 0.945 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.40 (br, 1H), 7.78 (s, 1H), 7.12 (d, J = 7.0 Hz, 1H), 6.92 (s, 1H), 6.50 (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.8, 153.8, 149.4, 134.0, 126.8, 120.0, 107.0, 106.3, 56.5, 56.3; HRMS (CI) calcd for $C_{11}H_{12}NO_3$ (M + 1) 206.0772, found 206.0739.

4-Bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one (23): To a stirred solution of 6,7-dimethoxyisoquinolin-1(2*H*)-one (**22**) (205 mg, 1 mmol) in glacial acetic acid (1.2 mL) at room temperature was added dropwise a solution of Br_2 (51 μL, 1 mmol) in glacial acetic acid (760 μL). The mixture was stirred for 1 h at room temperature. The reaction mixture was poured into ice−water and extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated to dryness to afford **23** in 96% yield (271 mg, 0.96 mmol): ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.45 (br, 1H) 7.62 (s, 1H), 7.44 (s, 1H), 7.12 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 160.3, 153.6, 149.2, 130.9, 128.0, 120.0, 107.5, 106.0, 97.1, 55.7; HRMS (CI) calcd for $C_{11}H_{11}BrNO_3$ (M + 1) 283.9878, found 283.9846.

6,7-Dimethoxy-4-phenylisoquinolin-1(2*H*)-one (24): To a mixture of 4-bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one (**23**) (100 mg 0.35 mmol), phenylboronic acid (64.6 mg, 0.52 mmol), Cs_2CO_3 (84.5 mg, 0.26 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (7.2 mg, 0.007 mmol, 2 mol %), and PA-Ph (4.1 mg, 0.014 mmol, 4 mmol %) was added toluene (3 mL). The reaction mixture was degassed, placed under an argon atmosphere, then irradiated in a microwave for 30 min at 90 °C. Toluene was evaporated under a reduced pressure and the residue was purified by flash column chromatography on silica gel with ethyl acetate as the eluent to give **24** in 98% yield (96 mg, 0.34 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.27 (br, 1H), 7.88 (s, 1H), 7.41−7.48 (m, 5H), 7.14 (s, 1H), 7.00 (s, 1H), 4.04 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.4, 153.7, 149.2, 136.9, 133.1, 129.9, 128.9, 127.8, 125.8, 119.9,

107.4, 105.3, 56.4, 56.1; HRMS (ES) calcd for $C_{17}H_{16}NO_3$ (M + 1) 282.1130, found 282.1291

6,7-Dimethoxy-1-oxo-1,2-dihydroisoquinoline-4-carbonitrile (25): To solution of 4-bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one (**23**) (0.96 mmol, 270.7 mg) in *N*-methyl-2-pyrrolidone (4 mL) was added (193.8 mg, 2 mmol) CuCN. The mixture was irradiated in a microwave for 40 min at 200 °C. The reaction mixture was concentrated under a reduced pressure and the residue was purified by flash column chromatography on silica gel with a gradient of 50% ethyl acetate in hexane to 100% ethyl acetate. Compound **25** was obtained in 86% yield (198 mg, 0.86 mmol): ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.08 (s, 1H), 7.58 (s, 1H), 7.02 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 160.5, 154.2, 149.6, 138.4, 129.2, 118.7, 116.7, 107.4, 103.9, 87.9, 56.0, 55.8; HRMS (CI) calcd for $C_{12}H_{11}N_2O_3$ (M + 1) 231.0725, found 231.0773.

1-Bromo-6,7-dimethoxy-4-phenylisoquinoline (26): To a mixture of 6,7-dimethoxy-4-phenylisoquinolin-1(2*H*)-one (**24**) (80 mg, 0.28 mmol) and $POBr_3$ (253.7 mg, 0.84 mmol) in a microwave vial was added DCM (3 mL). The mixture was irradiated in a microwave for 30 min at 120 °C. The reaction mixture was diluted with DCM (10 mL) and washed with saturated aqueous sodium bicarbonate solution (5 mL), then with brine (5 mL). The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure to give 1-bromo-6,7-dimethoxy-4-phenylisoquinoline (**26**) (98%), which was used for the synthesis of **27** and **28** without further purification.

6,7-Dimethoxy-1,4-diphenylisoquinoline (27): To a mixture of 1-bromo-6,7-dimethoxy-4-phenylisoquinoline (**26**) (0.107 mmol, 36.7 mg), phenylboronic acid (0.161 mmol, 16.6 mg), Cs_2CO_3 (0.24 mmol, 78.2 mg), $Pd_2(dba)_3 \cdot CHCl_3$ (2.3 mg, 0.0021 mmol, 2 mol %), and PA-Ph, (1.3 mg. 0.0043 mmol, 4 mmol %) was added toluene (1.5 mL). The mixture was degassed, placed under an argon atmosphere, then irradiated in a microwave for 30 min at 90 °C. Toluene was removed and the residue was purified by flash column chromatography on silica gel with ethyl acetate to give **27** in 95% yield (35 mg, 0.10 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.43 (s, 1H), 7.73 (d, J = 1.2 Hz, 2H), 7.45−7.57 (m, 8H), 7.25 (d, J = 1.2 Hz, 2H), 3.88 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.8, 152.7, 149.9, 141.5, 140.2, 137.9, 132.1, 131.6, 130.1, 129.8, 128.9, 128.6, 128.0, 122.6, 106.0, 103.6, 56.1; HRMS (ES) calcd for $C_{23}H_{19}NO_2$ (M + 1) 342.1494, found 342.1482.

6,7-Dimethoxy-4-phenyl-1-(piperidin-1-yl)isoquinoline (28): To a mixture of 1-bromo-6,7-dimethoxy-4-phenylisoquinoline (**26**) (36 mg, 0.1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.3 mg, 0.0021 mmol, 2 mol %), PA-Ph (1.3 mg. 0.0043 mmol, 4 mmol %), and NaO^{t}Bu, (14.4 mg, 0.15) in a microwave vial was added toluene (2 mL). The mixture was degassed with and placed under an atmosphere of argon. Piperidine (15 μL, 0.15 mmol) was added and the mixture was irradiated in a microwave for 30 min at 180 °C. Toluene was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel with 2% MeOH in DCM to yield **28** in 64% yield (22 mg, 0.064 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.01 (s, 1H), 7.50 (s, 5H), 7.14 (s, 2H), 4.04 (s, 3H), 3.84 (s, 3H), 3.33 (t, J = 5 Hz, 4H), 1.86 (m, 4H), 1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.9, 152.3, 149.0, 139.9, 138.3, 132.9, 130.1, 128.7, 127.8, 127.4, 117.4, 104.8, 104.1, 55.8, 52.7, 26.6, 25.0; HRMS (ES) calcd for $C_{22}H_{25}N_2O_2$ (M + 1) 349.1916, found 349.1935.

4-Bromo-1-chloro-6,7-dimethoxyisoquinoline (29): 4-Bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one (**23**) (283 mg, 1 mmol) was treated with $POCl_3$ (2 mL, 20 mmol) and then irradiated in a microwave for 30 min at 100 °C. The solvent was removed under reduced pressure and the residue was poured onto ice, made basic to pH 8, and extracted with DCM (3 × 10 mL). The DCM extract was dried over Na_2SO_4 and concentrated to give **29** in 98% yield (296 mg, 0.98 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.29 (s, 1H), 7.44 (s, 1H), 7.31 (s, 1H), 4.07 (s, 3H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.5, 151.6, 148.5, 141.6, 132.9, 123.3, 117.4, 105.0, 104.7, 56.4; HRMS (ES) calcd for $C_{11}H_{10}BrClNO_2$ (M + 1) 301.9583, found 301.9609.

4-Bromo-1-ethoxy-6,7-dimethoxyisoquinoline (30): To a solution of 4-bromo-1-chloro-6,7-dimethoxyisoquinoline (**29**) (50 mg, 0.17 mmol) in ethanol (2 mL) was added NaOEt (46.7 mg, 0.33 mmol). The reaction mixture was irradiated in a microwave for 30 min at 90 °C. The mixture was diluted with DCM (10 mL) and washed with distilled water (5 mL). The DCM was dried over Na_2SO_4. Removal of the solvent and purification by flash column chromatography on silica gel with 20% ethyl acetate in hexane yielded **30** in 87% yield (45 mg, 0.144 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (s, 1H), 7.5 (s, 1), 7.31 (s, 1H), 4.52 (q, J = 6.6 Hz, 2H), 4.06 (s, 3H), 4.04 (s, 3H), 1.50 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.1, 153.6, 150.1, 139.8, 132.7, 115.6, 110.3, 105.1, 103.3, 62.4, 56.3, 14.8; HRMS (EI) calcd for $C_{13}H_{14}BrNO_3$ 311.0157, found 311.0154.

1-Ethoxy-6,7-dimethoxy-4-phenylisoquinoline (31): By using 4-bromo-1-ethoxy-6,7-dimethoxyisoquinoline (**30**) (30 mg, 0.096 mmol) and phenylboronic acid (17.9 mg, 0.144 mmol) and the procedure as described for compound **24**, 1-ethoxy-6,7-dimethoxy-4-phenylisoquinoline (**31**) was obtained in 93% yield (29 mg, 0.092 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.81 (s, 1H), 7.58 (s, 1H), 7.47 (s, 5H), 7.10 (s, 1H), 4.58 (q, J = 6.8 Hz, 2H), 4.03 (s, 3H), 3.83 (s, 3H), 1.52 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.1, 152.7, 149.3, 138.3, 138.1, 132.7, 130.0, 128.6, 127.3, 126.9, 114.2, 103.7, 103.1, 62.0, 56.1, 55.9, 14.9; HRMS (ES) calcd for $C_{19}H_{20}NO_3$ (M + 1) 310.1443, found 310.1437.

1-Bromo-6,7-dimethoxyisoquinoline-4-carbonitrile (32): To a mixture of 6,7-dimethoxy-1-oxo-1,2-dihydroisoquinoline-4-carbonitrile (**25**) (150.1 mg, 0.652 mmol) and $POBr_3$ (0.59 g, 1.956 mmol) was added dicholoromethane (4 mL). The reaction mixture was irradiated in a microwave for 30 min at 150 °C. The anisole was removed under reduced pressure and the residue was added slowly to ice then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with saturated aqueous bisodium carbonate solution (5 mL), then with brine (5 mL). The organic extract was dried over Na_2SO_4 then concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel with CH_2Cl_2 to yield **32** in 89% yield (169 mg, 0.58 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.49 (s, 1H), 7.58 (s, 1H), 7.35 (s, 1H), 4.12 (s, 3H), 4.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.9, 152.6, 147.4, 145.7, 133.0, 124.4, 116.1, 107.5, 104.8, 103.0, 57.0, 56.6; HRMS (CI) calcd for $C_{12}H_{10}BrN_2O_2$ (M + 1) 292.9881, found 292.9902.

General Procedure for Coupling of 1-Bromo-6,7-dimethoxyisoquinoline-4-carbonitrile with Aldehydes via Nucleophilic Aroylation. To a stirred solution of 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile (**32**) (30.1 mg, 0.102 mmol), aldehyde (0.15 mmol), and (0.15 mmol) of 1,3-dimethylimidazolium iodide in DMF (1.5 mL) was added (0.15 mmol) NaH. The mixture was stirred at room temperature. After 2 h, water (4 mL) was added and the reaction mixture was extracted with chloroform (3 × 8 mL). The organic layer was dried over Na_2SO_4, then concentrated and the residue was purified by flash column chromatography on silica gel with a gradient of CH_2Cl_2 to 50% ethyl acetate in CH_2Cl_2 to afford the coupled product. **6,7-Dimethoxy-1-(4-methoxyphenylcarbonyl)isoquinoline-4-carbonitrile (33):** Using 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile (**32**) (30.1 mg, 0.102 mmol) and 4-methoxybenzaldehyde (20 mg, 0.15 mmol) and the procedure described above yielded **33** in 99% yield (35 mg, 0.102 mmol): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.79 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.50 (s, 1H), 7.44 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 4.12 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.7, 164.7, 157.2, 155.7, 152.2, 150.2, 145.2, 133.4, 128.9, 122.0, 116.5, 114.1, 105.6, 104.8, 102.7, 56.8, 56.5, 55.8; HRMS (CI) calcd for $C_{20}H_{17}N_2O_4$ (M + 1) 349.1144, found 349.1153.

6,7-Dimethoxy-1-phenylisoquinoline-4-carbonitrile (36): Using the cross-coupling procedure described for compound **24** with 1-bromo-6,7-dimethoxyisoquinoline-4-carbonitrile 32 (20 mg, 0.068 mmol) and phenylboronic acid (13 mg, 0.102 mmol) yielded 6,7-dimethoxy-1-phenylisoquinoline-4-carbonitrile **36** in 95% yield (19 mg, 0.065 mmol): ^{1}H NMR (CD_3OD, 200 MHz) δ 8.76 (s, 1H), 7.56−7.71 (m, 5H), 7.44 (d, J = 7.6 Hz, 2H), 4.11 (s, 3H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.9, 154.7, 151.2, 146.4, 138.7, 135.6, 133.3, 132.7, 129.6, 128.7, 128.0, 121.8, 117.0, 106.3, 102.8, 56.6, 56.1; HRMS (ES) calcd for $C_{18}H_{14}N_2O_2$ (M + 1) 291.1134, found 291.1143.

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Supporting Information Available: Preparative methods and characterization of compounds not described in the Experimental Section along with the ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.